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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,294	05/31/2006	Revel Michel	REVEL17	3323

1444 7590 10/07/2011

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EXAMINER	
WANG, CHANG YU	
ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
10/07/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,294	MICHEL ET AL.	
	Examiner	Art Unit	
	CHANG-YU WANG	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1,3,5,7,8 and 55-61* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1, 3, 5, 7, 8 and 55-61* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/2/11*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RESPONSE TO AMENDMENT

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/10/11 has been entered.

Status of Application/Amendments/claims

2. Applicant's amendment filed 8/10/11 is acknowledged. Claims 2, 4, 6, and 9-54 are cancelled. Claim 1 is amended. Claims 1, 3, 5, 7, 8 and 55-61 are pending in this application and under examination in this office action.

3. Applicant's arguments filed on 8/10/11 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections/Objections Withdrawn

3. The rejection of claim 54 under 35 U.S.C. 112, second paragraph, as being indefinite is moot because the claim is canceled.

Claim Rejections/Objections Maintained

In view of the amendment filed on 8/10/11, the following rejections are maintained.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 5, 7, 8 and 55-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gearhart et al. (US Patent No. 6562619, issued on May 13, 2003, priority Mar 31, 1998, cited previously) in view of Haggiag et al. (FEBS Letters, 1999. 457: 200-204) and Zhang et al. (Nat Biotechnol. 2001, Dec, 1129-1133, as in IDS) as evidenced by Baumann et al. (Physol. Rev. 2001. 81:871-927) and Billon et al. (J. Cell Sci. 2002. 115: 3657-3665, as in IDS) and Billon et al. (J. Cell Sci. 2002. 115: 3657-3665, as in IDS).

Claims 1, 3, 5, 7, 8 and 55-61 are drawn to a method of generating $O1^+$ and/or $O4^+$ oligodendrocytes comprising growing neurosphere (NS) cells in a culture medium that promotes preferential differentiation of NS cells into $O1^+$ and/or $O4^+$ oligodendrocytes, said culture medium comprising one or more gp130 activators selected from the group consisting of CNTF, oconstatin-M (OSM) or IL-6, IL6R/IL6 chimera and IL-11 and wherein said culture medium specifically enhances differentiation into O1+ and/or O4+ oligodendrocyte lineage, thereby causing the NS cells to preferentially differentiate along the oligodendrocyte lineage into O1+ and/or O4+ oligodendrocyte lineage. Dependent claims 60 and 61 are directed to one or more gp130 activator including IL6R/IL6 chimera is the only growth or differentiation agent and dependent claims 56 and 57 are directed to the culture medium promotes myelinating activity and formation of large and highly branched O+ and/or O4+ oligodendrocytes exhibiting large myelin membranes.

Gearhart et al. (US 6562619 or the '619 patent) teaches a method of differentiating oligodendrocytes comprising growing embryonic stem (pPS) cells including mouse and

human embryonic stem cells in the presence of a gp130 activator including IL-6 and IL-11 as recited in instant claims (see col. 28, example 6; col. 30, claims 1-28, in particular). Gearhart et al. teach that embryonic stem (ES) cells cultured in the standard culture medium form embryoid bodies (see col.. 29, lines 29-40; col.30, claim 9). Gearhart et al. teach that embryoid bodies are allowed to replate in insulin-transferin-selenium-fibronectin (ITSN) supplemented medium dissociated and replated into medium containing basic fibroblast growth factor (bFGF) (col. 15, lines 16-col. 16, line9, in particular). Gearhart et al. teach that upon removal of FGF, neurons, astrocytes, and oligodendrocytes are expected to form in situ. Further, Gearhart et al. teach that the culture medium for differentiation in the method of Gearhart contains FGF, LIF and IL-6 or IL-11(see col. 28, example 6; col. 30, claims 1-28, col. 14, line 27-col. 15, line 4 in particular). Gearhart et al. also teach a method of generating oligodendrocytes comprising growing human embryonic stem cells in the presence of a gp130 activator including a oncostatin-M (OSM) or LIF as recited in instant claims (see p. 237, abstract; p. 237, 2nd col.-p. 238, 1st col., in particular). Note that LIF, oncostatin-M (OSM), IL-6 or IL-11 is a gp130 activator as recited in instant claims 1, 3, and 60. But Gearhart et al. do not teach IL6R/IL6 chimera as in claims 1 and 61 and do not teach neurosphere (NS) cells and oligodendrocyte marker O1+ and/or O4+ as in claims 1, 7, 8, 57 and 60.

Although Gearhart et al. do not teach IL6R/IL6 chimera for gp130 activator, Haggiag et al. teach IL6R/IL6 chimera induces myelin gene expression in Schwann cells (i.e. glial cells of the PNS vs. oligodendrocytes (i.e. glial cells of the CNS) and dorsal root ganglia and activate gp130 signaling (see p. 200, abstract, in particular).

Thus, it is obvious to use IL6R/IL6 chimera as another gp130 activator to replace the OSM, IL6 or IL-11 in the method of Gearhart et al. for generating O1+ and/or O4+ oligodendrocytes because IL6R/IL6 chimera has been shown to act as an gp130 activator and induce myelin gene expression in Schwann cells as in claims 56 and 57.

Although Gearhart et al. do not explicitly teach neurospheres derived from embryoid bodies, the cells disclosed by Gearhart et al. are re-suspended and passaged through 1-3 passages (7 to 30 days) (col. 24-25, examples 1-2 and 6, in particular). The cell suspension re-cultured and replated can form neurospheres. Thus, the method of Gearhart et al. is to grow neurospheres because these re-passaged cells from embryoid bodies can form neurospheres and are neurospheres derived from embryoid bodies as evidenced by Zhang et al. (see p. 1129-1130, Nat Biotechnol. 2001, Dec, 1129-1133, cited previously).

Zhang et al. teach that human embryonic stem (ES) cells cultured in a defined medium containing FGF-2 (bFGF) for a week differentiate into O4+, O1+ and GFAP+ neural precursor cells (see p. 1130, 2nd col., in particular). Zhang further teaches that when continuing exposure to FGF-2, the above isolated human ES-derived neural precursor cells can form columar rosette cells (i.e. embryoid bodies). In addition, Zhang teaches that when the above cells were expending as free-floating cell aggregates in a suspension culture, these human ES-derived neurospheres can be maintained up to 8 passages and can be differentiated into neurons and glia in a similar pattern as early passages. Zhang further teaches that upon removal of FGF-2 (bFGF), the above cells can be differentiated into neurons, glia and oligodendrocytes (see p. 1129, in particular).

Note that based on the teaching of Zhang, human derived-ES cells can form embryoid bodies and neurospheres in the culture of human ES cells in the presence of FGF-2 as evidenced by Billon et al. (see p. 3658, 2nd Col., 3rd paragraph-p. 3659, 1 st col., 2nd paragraph, in particular, J. Cell Sci. 2002.115: 3657-3665, as in IDS). Thus, the cells through 1-3 passages of re-dissociation, resuspension and repassages from embryoid bodies (i.e. originally derived from embryonic stem cells) taught by Gearhart et al. would also give rise to neurospheres because the cells cultured in the method of Gearhart et al. are re-suspended and passaged and cultured in the same manner as the cells in Zhang and are as in instant specification (col. 24-25, examples 1-2 and 6, in particular). Thus, the cells derived from embryoid bodies as taught by Gearhart et al. would have similar properties as neurospheres recited instant claim 1.

Although Gearhart et al. do not explicitly teach expression $O4^+$ and $O1^+$ markers on differentiated oligodendrocytes as recited in instant claims 1, 7, 8, 57 and 60, Zhang et al. teach that human embryonic stem (ES) cells cultured in a defined medium containing FGF-2 (bFGF) for a week differentiate into O4+, O1+ and GFAP+ neural precursor cells (see p. 1130, 2^{nd} col., in particular). In addition, the expression of these markers on differentiated oligodendrocytes is an intrinsic feature of differentiated oligodendrocytes as evidenced by Baumann et al. (see p. 875, 2^{nd} col, 2^{nd} -3^{rd} paragraphs, in particular, Physol. Rev. 2001. 81:871-927). Baumann teaches that markers of differentiated oligodendrocytes including O4+ and O1+ (see p. 875, 2^{nd} col, 2^{nd} -3^{rd} paragraphs, in particular).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to use neurospheres or human ES-derived neurospheres in the method of the '619 patent to generate O1+ and/or O4+ oligodendrocytes in the presence of a gp130 activator such as CNTF, OSM, LIF, IL-6, IL-11 or IL6R/IL6 chimera. The person of ordinary skill in the art would have been motivated to do so with an expectation of success because neurospheres can be derived from embryoid bodies from cultured human ES as taught by Zhang and the cells expanded and re-suspended from embryoid bodies that are originally derived from human ES cells in the presence of a gp130 activator such as CNTF, OSM, LIF, IL-6, IL-11 or IL6R/IL6 chimera can be differentiated into O1+ and/or O4+ oligodendrocytes as taught by Gearhart et al..

On p. 5-6 of the response, Applicant argues that in view of Zhang, a skilled artisan would not expect that the method of Gearhart would lead to specifically enhancing oligodendrocyte lineages because Zhang only teaches few O+ oligodendrocytes (no O1+ oligodendrocyte) are produced. Applicant's arguments have been fully considered but they are not persuasive.

Contrary to Applicant's arguments, the examiner asserts that Applicant's interpretation on Zhang is incorrect. The citation of Zhang is to support that cells that are resuspended and cultured from embryoid bodies are capable of forming neurospheres. In addition, the teaching of Zhang also supports that the cells derived from resuspension of embryoid bodies and cultured in the method of Gearhart are neurospheres and are capable of differentiate into oligodendrocytes. In fact, Gearhart

has already shown that cells derived from embyroid bodies through several passages are capable of differentiating into oligodendrocytes. In addition, it is known in the art that the mature oligodendrocytes express O1+/O4 markers. The expression of O1+ /O4+ markers on mature oligodendrocytes is evidenced by Baumann et al. as previously made of record (see p. 875, 2nd col, 2nd -3rd paragraphs, in particular, Physol. Rev. 2001. 81:871-927, cited previously). Baumann teaches that markers of differentiated oligodendrocytes including O4+ and O1+ (see p. 875, 2nd col, 2nd -3rd paragraphs, in particular). Note that Applicant cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

On p. 6-7 of the response, Applicant argues that

On p. 8 of the response, Applicant argues that the use of IL6R/IL6 chimera as a gp130 activator would not be obvious. Applicant's arguments have been fully considered but they are not persuasive.

Contrary to Applicant's arguments, although Gearhart et al. do not teach IL6R/IL6 chimera for a gp130 activator, Gearhart teaches the use of IL6,

Gearhart et al. teach that the culture medium for differentiation in the method of Gearhart contains FGF, LIF and IL-6 or IL-11(see col. 28, example 6; col. 30, claims 1-28, col. 14, line 27-col. 15, line 4 in particular). Gearhart et al. also teach a method of

generating oligodendrocytes comprising growing human embryonic stem cells in the presence of a gp130 activator including a oncostatin-M (OSM) or LIF as recited in instant claims (see p. 237, abstract; p. 237, 2nd col.-p. 238, 1st col., in particular). Note that LIF, oncostatin-M (OSM), IL-6 or IL-11 is a gp130 activator as recited in instant claims 1, 3, and 60.

Haggiag et al. teach IL6R/IL6 chimera induces myelin gene expression in Schwann cells (i.e. glial cells of the PNS vs. oligodendrocytes (i.e. glial cells of the CNS) and dorsal root ganglia and activate gp130 signaling (see p. 200, abstract, in particular). Thus, it is obvious to use IL6R/IL6 chimera as another gp130 activator to replace the OSM, IL6 or IL-11 in the method of Gearhart et al. for generating O1+ and/or O4+ oligodendrocytes because IL6R/IL6 chimera has been shown to act as an gp130 activator and induce myelin gene expression in Schwann cells as in claims 56 and 57.

but Greahart does not teach neurospheres because Greahart fails to teach neurospheres derived from embryoid bodies. Applicant argues that embryoid bodies derived from embryonic stem cells are not the same as neurospheres as supported by Carpenter. On p. 13 of the response, Applicant argues that Gearhart fails to disclose a method using a culture medium that promotes preferential differentiation into oligodendrocytes as claimed because Gearhart only teaches generalized differentiation and not how to obtain preferential differentiation into oligodendrocytes. Applicant argues that the methods of Gearhart result in a mixture of cells, which are different from those

in instant claims. Applicant argues that neurospheres are not necessarily present in the cells or methods of Gearhart. On p. 14 of the response, Applicant argues that the primary reference does not disclose expression of O1+ and O4+ markers on differentiated oligodendrocytes. Applicant's arguments have been fully considered but they are not persuasive.

In response, Applicant cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In this case, Gearhart (the '619 patent) teaches a method of differentiating oligodendrocytes comprising growing embryonic stem (pPS) cells including mouse and human embryonic stem cells in the presence of a gp130 activator including IL-6 and IL-11 as recited in instant claims (see col. 28, example 6; col. 30, claims 1-28, in particular). Gearhart teaches that embryonic stem (ES) cells cultured in a standard culture medium form embryoid bodies, the embryoid body cells were re-suspended and passaged through 1-3 passages (7 to 30 days), replated in insulin-transferin-selenium-fibronectin (ITSN) supplemented medium dissociated and replated into medium containing basic fibroblast growth factor (bFGF) (see col. 29, lines 29-40; col.30, claim 9; col. 24-25, examples 1-2 and 6; col. 15, lines 16-col. 16, line9, in particular). Gearhart teaches that upon removal of FGF, neurons, astrocytes, and oligodendrocytes are expected to form in situ, and that the culture medium for differentiation contains FGF, LIF and IL-6, IL-11, oncostatin-M (OSM) or LIF (i.e. a gp130 activator) (see col. 28,

example 6; col. 30, claims 1-28, col. 14, line 27-col. 15, line 4; see p. 237, abstract; p. 237, 2nd col.-p. 238, 1st col., in particular). Thus, Gearhart does teach a method of generating oligodendrocytes from cells derived from cultured human ES cells and the human ES-derived cells have been through several passages of dissociation resuspension, replating and culturing from embyroid bodies.

Although Gearhart does not explicitly teach neurospheres derived from embryoid bodies, Zhang et al. teach that human embryonic stem (ES) cells cultured in a defined medium containing FGF-2 (bFGF) for a week differentiate into O4+, O1+ and GFAP+ neural precursor cells (see p. 1129-1130, in particular). Zhang further teaches that when continuing exposure to FGF-2, the above isolated human ES-derived neural precursor cells can form columar rosette cells (i.e. embryoid bodies). In addition, Zhang teaches that when the above cells were expending as free-floating cell aggregates in a suspension culture, these human ES-derived neurosphere can be maintained up to 8 passages and can be differentiated into neurons and glia in a similar pattern as early passages. Zhang further teaches that upon removal of FGF-2 (bFGF), the above cells can be differentiated into neurons, glia and oligodendrocytes (see p. 1129, in particular). Note that based on the teaching of Zhang, human derived-ES cells can form embryoid bodies and neurospheres in the culture of human ES cells in the presence of FGF-2 as evidenced by Billon et al. (see p. 3658, 2nd Col., 3rd paragraph-p. 3659, 1 st col., 2nd paragraph, in particular, J. Cell Sci. 2002.115: 3657-3665, as in IDS). Thus, the cells through 1-3 passages of re-dissociation, resuspension and repassages from embryoid bodies (i.e. originally derived from embryonic stem cells) taught by Gearhart would also

give rise to neurospheres because the cells cultured in the method of Gearhart are re-suspended and passaged and cultured in the same manner as the cells in Zhang and as in instant specification (col. 24-25, examples 1-2 and 6, in particular). Thus, the cells derived from embryoid bodies as taught by Gearhart would have similar properties as neurospheres recited instant claim 1.

Although Gearhart does not explicitly teach expression $O4^+$ and $O1^+$ markers on differentiated oligodendrocytes as recited in instant claims 1, 7, 8, 57 and 60, Zhang et al. teach that human embryonic stem (ES) cells cultured in a defined medium containing FGF-2 (bFGF) for a week differentiate into O4+, O1+ and GFAP+ neural precursor cells (see p. 1129-1130, in particular) and the markers for differentiated oligodendrocytes include O4+ and O1+ as evidenced by Baumann et al. (see p. 875, 2^{nd} col, 2^{nd} -3^{rd} paragraphs, in particular, Physol. Rev. 2001. 81:871-927, cited previously). It would have been obvious to a skilled artisan at the time the instant invention was made to use neurospheres or human ES-derived neurospheres in the method of Gearhart to generate O1+ and/or O4+ oligodendrocytes in the presence of a gp130 activator such as CNTF, OSM, LIF, IL-6 or IL-11. The skilled artisan would have been motivated to do so with an expectation of success because neurospheres can be derived from embryoid bodies from cultured human ES as taught by Zhang and the cells expanded and re-suspended from embryoid bodies that are originally derived from human ES cells in the presence of a gp130 activator such as CNTF, OSM, LIF, IL-6 or IL-11 can be differentiated into O1+ and/or O4+ oligodendrocytes as taught by Gearhart.

The instant method is obvious over the cited references because the instant method is to simply replace "the cells derived from embryoid bodies" with "neurospheres" in the method of Gearhart because cells expanded or derived embyoid bodies would have similar properties derived from neurospheres and cells derived embryoid bodies cultured in a free-floating suspension would give rise to neurospheres. Thus, the results from the claimed are expected.

On p. 14-17 of the response, Applicant argues that Zhang does not disclose or suggest steps for the differentiation of ES cells toward specific cell lineages such as myelinated oligodendrocytes. Applicant argues that the instant invention is an improvement over the method in Zhang. Applicant argues that Zhang does not provide motivation to modify the method of Gearhart to solely use neurospheres in the claimed method. Applicant's arguments have been fully considered but they are not persuasive.

Contrary to Applicant's arguments, Zhang does teach steps for differentiation of human ES cells toward specific cell lineages such as O4+, O1+ oligodendrocytes (see p. 1129-1130, in particular). In addition, the Zhang reference is to support the cells in the method of Gearhart are capable of differentiating into O4+, O1+ oligodendrocytes and is also to support that human derived-ES cells can form embryoid bodies and neurospheres in the culture of human ES cells in the presence of FGF-2 in the method of Gearhart as evidenced by Billon et al. (see p. 3658, 2nd Col., 3rd paragraph-p. 3659, 1st col., 2nd paragraph, in particular, J. Cell Sci. 2002.115: 3657-3665, as in IDS).

On p. 17-18 of the response, Applicant argues that the gp130 activator does not exert the same effect on embryoid bodies as it does not neurospheres. Applicant argues that embryoid bodies treated with IL6RIL6 resulted in no expression of oligodendrocyte lineage-specific gene expression whiles neurospheres treated with IL6RIL6 resulted in marked increase in expression and cites example 5 of the specification (see p. 35-36) in support of the arguments. Applicant's arguments have been fully considered but they are not persuasive.

In response, Applicant's arguments regarding to no enhancement of specific gene expression in embryoid bodies when treated with a gp130 activator are irrelevant because the cells used in the method of Gearhart to differentiate into oligodendrocytes are not embryoid bodies. Instead, the cells used in the method of Gearhart are the cells derived from the embryoid body cells after culturing several passages of the cells dissociated from embryoid bodies. Although Gearhart does not explicitly use the term "neurospheres", embryoid bodies after dissociation, resuspension, replating and culturing several passages, the cells are called neurospheres and can be differentiated into neurons and glia in a similar pattern as early passages as supported by Zhang. Zhang teaches that columar rosette cells (i.e. embryoid bodies) cultured from human ES-derived neural precursor cells after expending as free-floating cell aggregates in a suspension culture are called human ES-derived neurospheres; and these human ES-derived neurosphere can be maintained up to 8 passages and can be differentiated into neurons and glia in a similar pattern as early passages.

On p. 18-19 of the response, Applicant argues that Gearhart relates to differentiation into a mixture of neuronal cells in general but does not teach the use of a culture medium in a method to specifically enhance differentiation to cause the NS cells to differentiate along the oligodendrocyte lineage into O1+ and/or O4+ oligodendrocytes. Applicant's arguments have been fully considered but they are not persuasive.

Contrary to Applicant's arguments, Gearhart does teach the culture medium for differentiation into oligodendrocytes wherein the medium contains FGF, LIF and IL-6 or IL-11(see col. 28, example 6; col. 30, claims 1-28, col. 14, line 27-col. 15, line 4 in particular). Gearhart also teaches a method of differentiating oligodendrocytes comprising growing embryonic stem (pPS) cells including mouse and human embryonic stem cells in the presence of a gp130 activator including IL-6, IL-11, LIF, or oncostatin-M as recited in instant claims (see col. 28, example 6; col. 30, claims 1-28, in particular).). In particular, Gearhart teaches that upon removal of FGF, neurons, astrocytes, and oligodendrocytes are expected to form in situ (col. 15, lines 16-col. 16, line9; see col. 28, example 6; col. 30, claims 1-28, col. 14, line 27-col. 15, line 4 in particular). Note that the instant claims are not limited to generate a specific proportion of O1+/O4+ oligodendrocytes. As long as the method of Gearhart can generate oligodendrocytes that are O1 and/or O4 positive, the teaching of Gearhart meets the limitations recited in instant claims. In addition, although Gearhart does not explicitly teach that

oligodendrocytes are O4+ and O1+, Baumann teaches that markers of differentiated oligodendrocytes including O4+ and O1+ (see p. 875, 2nd col, 2nd -3rd paragraphs, in particular) and Zhang teaches that human embryonic stem (ES) cells cultured in a defined medium containing FGF-2 (bFGF) for a week differentiate into O4+, O1+ and GFAP+ neural precursor cells (see p. 1129-1130, in particular). Thus, Gearhart does teach a culture medium for differentiation of oligodendrocytes.

On p. 18-19 of the response, Applicant argues that the combination of Gearheart and Zhang fails to disclose or suggest each and every element of the claims. Applicant argues that the references of Bauman and Billon do not resolve the deficiencies of Gearhart and Zhan because Billon relates to a study of timing of oligodendrocyte development from genetically engineered-selectable mouse ES cells and Billon does not teach the use of neurospheres. Applicant's arguments have been fully considered but they are not persuasive.

In response, Applicant cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In this case, Gearhart (the '619 patent) teaches a method of differentiating oligodendrocytes comprising growing embryonic stem (pPS) cells including mouse and human embryonic stem cells in the presence of a gp130 activator including IL-6 and IL-11 as recited in instant claims (see col. 28, example 6; col. 30, claims 1-28, in particular). Gearhart teaches that embryonic stem (ES) cells cultured in a standard

culture medium form embryoid bodies (see col. 29, lines 29-40; col.30, claim 9). Gearhart teaches that the embryoid body cells were re-suspended and passaged through 1-3 passages (7 to 30 days) (col. 24-25, examples 1-2 and 6, in particular) and replated in insulin-transferin-selenium-fibronectin (ITSN) supplemented medium dissociated and replated into medium containing basic fibroblast growth factor (bFGF) (col. 15, lines 16-col. 16, line9, in particular). Gearhart teaches that upon removal of FGF, neurons, astrocytes, and oligodendrocytes are expected to form in situ, and that the culture medium for differentiation contains FGF, LIF and IL-6, IL-11, oncostatin-M (OSM) or LIF (i.e. a gp130 activator) (see col. 28, example 6; col. 30, claims 1-28, col. 14, line 27-col. 15, line 4; see p. 237, abstract; p. 237, 2nd col.-p. 238, 1st col., in particular)

Although Gearhart does not explicitly teach neurospheres derived from embryoid bodies, Zhang et al. teach that human embryonic stem (ES) cells cultured in a defined medium containing FGF-2 (bFGF) for a week differentiate into O4+, O1+ and GFAP+ neural precursor cells (see p. 1129-1130, in particular). Zhang further teaches that when continuing exposure to FGF-2, the above isolated human ES-derived neural precursor cells can form columar rosette cells (i.e. embryoid bodies). In addition, Zhang teaches that when the above cells were expending as free-floating cell aggregates in a suspension culture, these human ES-derived neurosphere can be maintained up to 8 passages and can be differentiated into neurons and glia in a similar pattern as early passages. Zhang further teaches that upon removal of FGF-2 (bFGF), the above cells can be differentiated into neurons, glia and oligodendrocytes (see p. 1129, in particular).

Note that based on the teaching of Zhang, human derived-ES cells can form embryoid bodies and neurospheres in the culture of human ES cells in the presence of FGF-2 as evidenced by Billon et al. (see p. 3658, 2nd Col., 3rd paragraph-p. 3659, 1 st col., 2nd paragraph, in particular, J. Cell Sci. 2002.115: 3657-3665, as in IDS). Thus, the cells through 1-3 passages of re-dissociation, resuspension and repassages from embryoid bodies (i.e. originally derived from embryonic stem cells) taught by Gearhart would also give rise to neurospheres because the cells cultured in the method of Gearhart are re-suspended and passaged and cultured in the same manner as the cells in Zhang and as in instant specification (col. 24-25, examples 1-2 and 6, in particular). Thus, the cells derived from embryoid bodies as taught by Gearhart would have similar properties as neurospheres recited instant claim 1.

Although Gearhart does not explicitly teach expression $O4^+$ and $O1^+$ markers on differentiated oligodendrocytes as recited in instant claims 1, 7, 8, 57 and 60, Zhang et al. teach that human embryonic stem (ES) cells cultured in a defined medium containing FGF-2 (bFGF) for a week differentiate into O4+, O1+ and GFAP+ neural precursor cells (see p. 1129-1130, in particular) and the markers for differentiated oligodendrocytes include O4+ and O1+ as evidenced by Baumann et al. (see p. 875, 2^{nd} col, 2^{nd} -3^{rd} paragraphs, in particular, Physol. Rev. 2001. 81:871-927, cited previously). It would have been obvious to a skilled artisan at the time the instant invention was made to use neurospheres or human ES-derived neurospheres in the method of Gearhart to generate O1+ and/or O4+ oligodendrocytes in the presence of a gp130 activator such as CNTF, OSM, LIF, IL-6 or IL-11. The skilled artisan would have been motivated to do

so with an expectation of success because neurospheres can be derived from embryoid bodies from cultured human ES as taught by Zhang and the cells expanded and re-suspended from embryoid bodies that are originally derived from human ES cells in the presence of a gp130 activator such as CNTF, OSM, LIF, IL-6 or IL-11 can be differentiated into O1+ and/or O4+ oligodendrocytes as taught by Gearhart.

The instant method is obvious over the cited references because the instant method is to simply replace "the cells derived from embryoid bodies" with "neurospheres" in the method of Gearhart because cells expanded or derived embyoid bodies would have similar properties derived from neurospheres and cells derived embryoid bodies cultured in a free-floating suspension would give rise to neurospheres. Thus, the results from the claimed are expected. Obviousness is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR International Co. V. Teleflex Inc. 82 USPQ2d 1385 (2007). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Conclusion

5. NO CLAIM IS ALLOWED.

6. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang, Ph.D. whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday from 8:30 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at (571) 272-0911.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chang-Yu Wang
September 29, 2011

/Chang-Yu Wang/
Primary Examiner, Art Unit 1649